Lescol® XL (fluvastatin sodium) Extended-Release Tablets
80 mg
Yellow, round, slightly biconvex film-coated tablet with beveled edges debossed with "Lescol XL" on one side and "80" on the other.
Bottles of 30 tablets ..... (NDC 0078-0354-15)
Bottle of 100 tablets ..... (NDC 0078-0354-05)
Store and Dispense
Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature]. Dispense in a tight container. Protect from light.

*Trademark of Medical Economics Company, Inc.

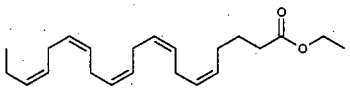
T2003-40
REV: MAY 2003 89011106
Shown in Product Identification Guide, page 331

OMACOR®

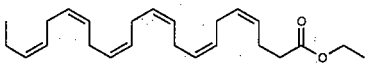
[ō-mă-kōr]
(omega-3-acid ethyl esters) Capsules

DESCRIPTION

Omacor, a lipid-regulating agent, is supplied as a liquid-filled gel capsule for oral administration. Each one gram capsule of Omacor (omega-3 acid ethyl esters) contains at least 900 mg of the ethyl esters of omega-3 fatty acids. These are predominantly a combination of ethyl esters of eicosapentaenoic acid (EPA - approximately 465 mg) and docosahexaenoic acid (DHA - approximately 375 mg).
The structural formula of EPA ethyl ester is:



The empirical formula of EPA ethyl ester is $C_{22}H_{34}O_2$, and the molecular weight of EPA ethyl ester is 330.51.
The structural formula of DHA ethyl ester is:



The empirical formula of DHA ethyl ester is $C_{24}H_{36}O_2$, and the molecular weight of DHA ethyl ester is 356.55.
Omacor capsules also contain the following inactive ingredients: 4 mg α-tocopherol (in a carrier of partially hydrogenated vegetable oils including soybean oil), and gelatin, glycerol, and purified water (components of the capsule shell).

CLINICAL PHARMACOLOGY

Mechanism of Action
The mechanism of action of Omacor is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase and increased peroxisomal β-oxidation in the liver. Omacor may reduce the synthesis of triglycerides (TGs) in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.
Pharmacokinetic and Bioavailability Studies
In healthy volunteers and in patients with hypertriglyceridemia (HTG), EPA and DHA were absorbed when administered as ethyl esters orally. Omega-3-acids administered as ethyl esters (Omacor) induced significant, dose–dependent increases in serum phospholipid EPA content, though increases in DHA content were less marked and not dose-dependent when administered as ethyl esters. Uptake of EPA and DHA into serum phospholipids in subjects treated with Omacor was independent of age (<49 years vs. ≥49 years). Females tended to have more uptake of EPA into serum phospholipids than males. Pharmacokinetic data on Omacor in children are not available.
Drug Interactions
Cytochrome P450-Dependent Monooxygenase Activities
The effect of a mixture of free fatty acids (FFA), EPA/DHA and their FFA-albumin conjugate on cytochrome P450-dependent monooxygenase activities was assessed in human liver microsomes. At the 23 μM concentration, FFA resulted in a less than 32% inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A. At the 23 μM concentration, the FFA-albumin conjugate resulted in a less than 20% inhibition of CYP2A6, 2C19, 2D6, and 3A, with a 68% inhibition being seen for CYP2E1. Since the free forms of the EPA and DHA are undetectable in the circulation (<1 μM), clinically significant drug-drug interactions due to inhibition of P450 mediated metabolism EPA/DHA combinations are not expected in humans.

CLINICAL STUDIES

The effects of Omacor 4 g per day were assessed in two randomized, placebo-controlled, double-blind, parallel-group studies of 84 adult patients (42 on Omacor, 42 on placebo) with very high triglyceride levels (Table 1). Patients whose baseline triglyceride levels were between 500 and 2000 mg/dL were enrolled in these two studies of 6 and 16 weeks duration. The median triglyceride and LDL-C levels in these patients were 792 mg/dL and 100 mg/dL, respectively. Median HDL-C level was 23.0 mg/dL.
(See table 1 above)

Table 1. Median Baseline and Percent Change From Baseline in Lipid Parameters in Patients with Very High TG Levels (≥ 500 mg/dL)

	TG		LDL-C		CHOL		HDL-C		VLDL-C		non-HDL-C	
	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg	BL	% Chg
Placebo	788	+6.7	108	-4.8	314	-1.7	24	0.0	175	-0.9	292	-3.6
Omacor 4g/day	816	-44.9	89	+44.5	296	-9.7	22	+9.1	175	-41.7	271	-13.8
Difference		-51.6		+49.3		-8.0		+9.1		-40.8		-10.2

BL = Baseline (mg/dL); % Chg = Percent Change from Baseline; Difference = Omacor - Placebo

Table 2. Adverse Events in Randomized, Placebo-Controlled, Double-Blind, Parallel-Group Studies for Hypertriglyceridemia That Used Omacor 4 g per Day

BODY SYSTEM Adverse Event	Omacor (N = 226)		Placebo* (N = 228)	
	n	%	n	%
Subjects with at least 1 adverse event	80	35.4	63	27.6
Body as a whole				
Back pain	5	2.2	3	1.3
Flu syndrome	8	3.5	3	1.3
Infection	10	4.4	5	2.2
Pain	4	1.8	3	1.3
Cardiovascular				
Angina pectoris	3	1.3	2	0.9
Digestive				
Dyspepsia	7	3.1	6	2.6
Eructation	11	4.9	5	2.2
Skin				
Rash	4	1.8	1	0.4
Special senses				
Taste perversion	6	2.7	0	0.0

Adverse events were coded using COSTART, version 5.0. Subjects were counted only once for each body system and for each preferred term.
*Placebo was corn oil for all studies.

Omacor 4 g per day reduced median TG, VLDL-C, and non-HDL-C levels and increased median HDL-C from baseline relative to placebo. Omacor treatment to reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some individuals.
Patients should be monitored to ensure that the LDL-C level does not increase excessively.
The effect of Omacor on the risk of pancreatitis in patients with very high TG levels has not been evaluated. The effect of Omacor on cardiovascular mortality and morbidity in patients with very high TG levels has not been determined.

INDICATIONS AND USAGE

Omacor is indicated as an adjunct to diet to reduce very high (≥ 500 mg/dL) triglyceride (TG) levels in adult patients.
Usage Considerations
According to accepted clinical guidelines, excess body weight and excess alcohol intake may be important factors in hypertriglyceridemia (HTG) and should be addressed before initiating any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, (such as hypothyroidism or diabetes mellitus) should be looked for and adequately treated. Estrogen therapy, thiazide diuretics, and beta blockers are sometimes associated with massive rises in plasma TG levels. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy for HTG.
The use of lipid-regulating agents should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use lipid-regulating agents, the patient should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet. (See PRECAUTIONS).

CONTRAINDICATIONS

Omacor is contraindicated in patients who exhibit hypersensitivity to any component of this medication.

PRECAUTIONS

General
Initial Therapy
Laboratory studies should be performed to ascertain that the patient's TG levels are consistently abnormal before instituting Omacor therapy. Every attempt should be made to control serum TG levels with appropriate diet, exercise, weight loss in overweight patients, and control of any medical problems (such as diabetes mellitus and hypothyroidism) that may be contributing to the patient's TG abnormalities. Medications known to exacerbate HTG (such as beta blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before considering TG–lowering drug therapy.
Continued Therapy
Laboratory studies should be performed periodically to measure the patient's TG levels during Omacor therapy. Omacor therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment.
Information for Patients
Omacor should be used with caution in patients with known sensitivity or allergy to fish. Patients should be advised that use of lipid-regulating agents does not reduce the importance of adhering to diet.
Laboratory Tests
In some patients, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase (AST) levels were observed. Alanine aminotransferase levels should be monitored periodically during Omacor therapy. In some patients, Omacor increased low-density lipoprotein cholesterol (LDL-C) levels. As with any lipid-regulating product, LDL-C levels should be monitored periodically during Omacor therapy.
Drug Interactions
Anticoagulants
Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Omacor and concomitant anticoagulants. Patients receiving treatment with both Omacor and anticoagulants should be monitored periodically.
Cytochrome P450-Dependent Monooxygenase Activities
Omega-3-fatty acid containing products have been shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The potential of Omacor to induce P450 activities in humans has not been studied.
Carcinogenesis, Mutagenesis, Impairment of Fertility
In a rat carcinogenicity study with oral gavage doses of 100, 600, 2000 mg/kg/day by oral gavage, males were treated with omega-3-acid ethyl esters for 101 weeks and females for 89 weeks without an increased incidence of tumors (up to 5 times human systemic exposures following an oral dose of 4 g/day based on a body surface area comparison). Standard lifetime carcinogenicity bioassays were not conducted in mice.
Omega-3-acid ethyl esters were not mutagenic or clastogenic with or without metabolic activation in the bacterial mutagenesis (Ames) test with *Salmonella typhimurium* and *Escherichia coli* or in the chromosomal aberration assay in Chinese hamster V79 lung cells or human lymphocytes. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay.
In a rat fertility study with oral gavage doses of 100, 600, 2000 mg/kg/day, males were treated for 10 weeks prior to mating and females were treated for 2 weeks prior to and throughout mating, gestation and lactation. No adverse effect on fertility was observed at 2000 mg/kg/day (5 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. It is unknown whether Omacor can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Omacor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Omega-3-acid ethyl esters have been shown to have an embryocidal effect in pregnant rats when given in doses resulting in exposures 7 times the recommended human dose of 4 g/day based on a body surface area comparison.
In female rats given oral gavage doses of 100, 600, 2000 mg/kg/day beginning two weeks prior to mating and continuing through gestation and lactation, no adverse effects were observed in the high dose group (5 times human systemic exposure following an oral dose of 4 g/day based on body surface area comparison).

Continued on next page

Omacor—Cont.

In pregnant rats given oral gavage doses of 1000, 3000, 6000 mg/kg/day from gestation day 6 thorough 15, no adverse effects were observed (14 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).
In pregnant rats given oral gavage doses of 100, 600, 2000 mg/kg/day from gestation day 14 through lactation day 21, no adverse effects were seen at 2000 mg/kg/day (5 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, decreased live births (20% reduction) and decreased survival to postnatal day 4 (40% reduction) were observed in a dose-ranging study using higher doses of 3000mg/kg/day (7 times the human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).
In pregnant rabbits given oral gavage doses of 375, 750, 1500 mg/kg/day from gestation day 7 through 19, no findings were observed in the fetuses in groups given 375 mg/kg/day (2 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison). However, at higher doses, evidence of maternal toxicity was observed (4 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison).

Nursing Mothers

It is not known whether omega-3-acid ethyl esters are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Omacor is administered to a woman who is breastfeeding.

Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric Use

A limited number of patients over 65 years of age were enrolled in the clinical studies. In the pooled analyses, safety and efficacy findings in subjects over 60 years of age (approximately 25% of the study population) did not appear to differ from those of subjects less than 60 years of age.

ADVERSE REACTIONS

Treatment-emergent adverse events reported in at least 1% of patients treated with Omacor 4 g per day or placebo during 8 randomized, placebo-controlled, double-blind, parallel-group studies for HTG are listed in Table 2. Adverse events led to discontinuation of treatment in 3.5% of patients treated with Omacor and 2.6% of patients treated with placebo.
[See table 2 at top of previous page]
Additional adverse events reported by 1 or more patients from 22 clinical studies for HTG are listed below:
BODY AS A WHOLE: enlarged abdomen, asthenia, body odor, chest pain, chills, suicide, fever, generalized edema, fungal infection, malaise, neck pain, neoplasm, rheumatoid arthritis, sudden death, and viral infection.
CARDIOVASCULAR SYSTEM: arrhythmia, bypass surgery, cardiac arrest, hyperlipemia, hypertension, migraine, myocardial infarct, myocardial ischemia, occlusion, peripheral vascular disorder, syncope, and tachycardia.
DIGESTIVE SYSTEM: anorexia, constipation, dry mouth, dysphagia, colitis, fecal incontinence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, intestinal obstruction, melena, pancreatitis, tenesmus, and vomiting.
HEMATOLOGIC-LYMPHATIC SYSTEM: lymphadenopathy.
METABOLIC AND NUTRITIONAL DISORDERS: edema, hyperglycemia, increased ALT, and increased AST.
MUSCULOSKELETAL SYSTEM: arthralgia, arthritis, myalgia, pathological fracture, and tendon disorder.
NERVOUS SYSTEM: central nervous system neoplasia, depression, dizziness, emotional lability, facial paralysis, insomnia, vasodilatation, and vertigo.
RESPIRATORY SYSTEM: asthma, bronchitis, increased cough, dyspnea, epistaxis, laryngitis, pharyngitis, pneumonia, rhinitis, and sinusitis.
SKIN: alopecia, eczema, pruritis, and sweating.
SPECIAL SENSES: cataract.
UROGENITAL SYSTEM: cervix disorder, endometrial carcinoma, epididymitis, and impotence.

DRUG ABUSE AND DEPENDENCE

Omacor does not have any known drug abuse or withdrawal effects.

OVERDOSAGE

In the event of an overdose, the patient should be treated symptomatically, and general supportive care measures instituted, as required.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving Omacor, and should continue this diet during treatment with Omacor. In clinical studies, Omacor was administered with meals.
The daily dose of Omacor is 4 g per day. The daily dose may be taken as a single 4-g dose (4 capsules) or as two 2-g doses (2 capsules given twice daily).

HOW SUPPLIED

Omacor (omega-3-acid ethyl esters) capsules are supplied as 1-gram transparent soft-gelatin capsules filled with light-yellow oil and bearing the designation OMACOR in bottles of 60 (NDC 65726-424-15) and 120 (NDC 65726-424-27).

Recommended Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Do not freeze.
Keep out of reach of children.
Rx only
April 2005
Reliant
PHARMACEUTICALS, INC.
Distributed by:
Reliant Pharmaceuticals, Inc.
Liberty Corner, NJ 07938
Address Medical Inquiries to:
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Medical Affairs
110 Allen Road
Liberty Corner, NJ 07938

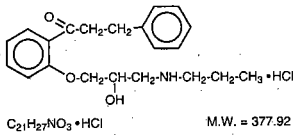
4241F-00 PRINTED IN USA
Shown in Product Identification Guide, page 331

RYTHMOL® SR ℞

[ryth-mul]
(propafenone hydrochloride) extended release CAPSULES

DESCRIPTION

RYTHMOL SR (propafenone hydrochloride) is an antiarrhythmic drug supplied in extended-release capsules of 225, 325 and 425 mg for oral administration.
The structural formula of propafenone HCl is given below:



$C_{21}H_{27}NO_3$ •HCl M.W. = 377.92

2'-[2-Hydroxy-3-(propylamino) -propoxy]-3-phenylpropiophenone hydrochloride

Propafenone HCl has some structural similarities to beta-blocking agents. Propafenone HCl occurs as colorless crystals or white crystalline powder with a very bitter taste. It is slightly soluble in water (20°C), chloroform and ethanol. Rythmol SR are capsules filled with cylindrical-shaped 2 × 2 mm microtablets containing propafenone and the following inactive ingredients: antifoam, gelatin, hypromellose, red iron oxide, magnesium stearate, shellac, sodium lauryl sulfate, sodium dodecyl sulfate, soy lecithin and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Propafenone is a Class 1C antiarrhythmic drug with local anesthetic effects, and a direct stabilizing action on myocardial membranes. The electrophysiological effect of propafenone manifests itself in a reduction of upstroke velocity (Phase 0) of the monophasic action potential. In Purkinje fibers, and to a lesser extent myocardial fibers, propafenone reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and effective refractory period prolonged. Propafenone reduces spontaneous automaticity and depresses triggered activity.
Studies in anesthetized dogs and isolated organ preparations show that propafenone has beta-sympatholytic activity at about 1/50 the potency of propranolol. Clinical studies employing isoproterenol challenge and exercise testing after single doses of propafenone indicate a beta-adrenergic blocking potency (per mg) about 1/40 that of propranolol in man. In clinical trials with the immediate release formulation, resting heart rate decreases of about 8% were noted at the higher end of the therapeutic plasma concentration range. At very high concentrations *in vitro*, propafenone can inhibit the slow inward current carried by calcium, but this calcium antagonist effect probably does not contribute to antiarrhythmic efficacy. Moreover, propafenone inhibits a variety of cardiac potassium currents in *in vitro* studies (i.e. the transient outward, the delayed rectifier, and the inward rectifier current). Propafenone has local anesthetic activity approximately equal to procaine. Compared to propafenone, the main metabolite, 5-hydroxypropafenone, has similar sodium and calcium channel activity, but about 10 times less beta-blocking activity (N-depropylpropafenone has weaker sodium channel activity but equivalent affinity for beta-receptors).

Electrophysiology:

Electrophysiology studies in patients with ventricular tachycardia (VT) have shown that propafenone prolongs atrioventricular (AV) conduction while having little or no effect on sinus node function. Both atrioventricular (AV) nodal conduction time (AH interval) and His-Purkinje conduction time (HV interval) are prolonged. Propafenone has little or no effect on the atrial functional refractory period, but AV nodal functional and effective refractory periods are prolonged. In patients with Wolff-Parkinson-White (WPW) syndrome, RYTHMOL immediate release tablets reduce conduction and increase the effective refractory period of the accessory pathway in both directions (see **ADVERSE REACTIONS/Electrocardiograms**).

Hemodynamics:

Studies in humans have shown that propafenone exerts a negative inotropic effect on the myocardium. Cardiac catheterization studies in patients with moderately impaired ventricular function (mean C.I.=2.61 L/min/m^2), utilizing intravenous propafenone infusions (loading dose of 2 mg/kg over 10 min+ followed by 2 mg/min for 30 min) that gave mean plasma concentrations of 3.0 µg/mL (a dose that produces plasma levels of propafenone greater than does recommended oral dosing), showed significant increases in pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances and depression of cardiac output and cardiac index.

Pharmacokinetics and Metabolism:

Absorption/Bioavailability

Maximal plasma levels of propafenone are reached between three to eight hours following the administration of RYTHMOL SR. Propafenone is known to undergo extensive and saturable presystemic biotransformation which results in a dose and dosage form dependent absolute bioavailability; e.g., a 150 mg immediate release tablet had an absolute bioavailability of 3.4%, while a 300 mg immediate release tablet had an absolute bioavailability of 10.6%. Absorption from a 300 mg solution dose was rapid, with an absolute bioavailability of 21.4%. At still larger doses, above those recommended, bioavailability of propafenone from immediate release tablets increased still further.
Relative bioavailability assessments have been performed between RYTHMOL SR capsules and RYTHMOL immediate release tablets. In extensive metabolizers, the bioavailability of propafenone from the SR formulation was less than that of the immediate release formulation as the more gradual release of propafenone from the prolonged-release preparations resulted in an increase in overall first pass metabolism (see **Metabolism**). As a result of the increased first pass effect, higher daily doses of propafenone were required from the SR formulation relative to the immediate release formulation, to obtain similar exposure to propafenone. The relative bioavailability of propafenone from the 325 twice daily regimens of RYTHMOL SR approximates that of RYTHMOL immediate release 150 mg three times daily regimen. Mean exposure to 5-hydroxypropafenone was about 20-25% higher after SR capsule administration than after immediate-release tablet administration.
Food increased the exposure to propafenone 4-fold after single dose administration of 425 mg of RYTHMOL SR. However, in the multiple dose study (425 mg dose BID), the difference between the fed and fasted state was not significant.

Distribution

Following intravenous administration of propafenone, plasma levels decline in a bi-phasic manner consistent with a two compartment pharmacokinetic model. The average distribution half-life corresponding to the first phase was about five minutes. The volume of the central compartment was about 88 liters (1.1 L/kg) and the total volume of distribution about 252 liters.
In serum, propafenone is greater than 95% bound to proteins within the concentration range of 0.5 - 2 µg/mL. Protein binding decreases to about 88% in patients with severe hepatic dysfunction.

Metabolism

There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life from 2-10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10-32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs such as encainide, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme. In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers.
As a consequence of the observed differences in metabolism, administration of RYTHMOL SR to slow and extensive metabolizers results in significant differences in plasma concentrations of propafenone, with slow metabolizers achieving concentrations about twice those of the extensive metabolizers at daily doses of 850 mg/day. At low doses the differences are greater, with slow metabolizers attaining concentrations about three to four times higher than extensive metabolizers. In extensive metabolizers, saturation of the hydroxylation pathway (CYP2D6) results in greater-than-linear increases in plasma levels following administration of RYTHMOL SR capsules. In slow metabolizers, propafenone pharmacokinetics are linear. Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolizers, and because steady-state conditions are achieved after four to five days of dosing in all patients, the recommended dosing regimen of RYTHMOL SR is the same for all patients. The large intersubject variability in blood levels require that the dose of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity (see **DOSAGE AND ADMINISTRATION**).
The 5-hydroxypropafenone and norpropafenone metabolites have electrophysiologic properties similar to propafenone *in*

vitro. In man after admin
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centrations less than 40%
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clearance, reaching 60-70%
below.
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RYTHMOL SR capsules, t
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325 and 425 mg RYTHMO
addition, no difference in t
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RAFT
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See table above]
There was a dose response
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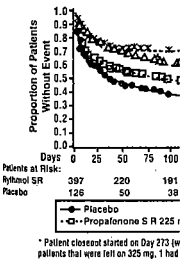
Figure 1: RAFT Kaplan-Meier Es
from Day 1 of randor



* Patient closeout started on Day 273 (w
patients that were felt on 325 mg, 1 had

In additional analyses, RYT
BID, and 425 mg BID) was
first recurrence of sympton
5 (steady-state pharmacok
arrhythmic effect of RYTH
age, gender, history of car
brillation, frequency of atr
tion that lowers heart rat
effect of RYTHMOL SR was
use of calcium channel blo

This information is intended for U.S. residents only.

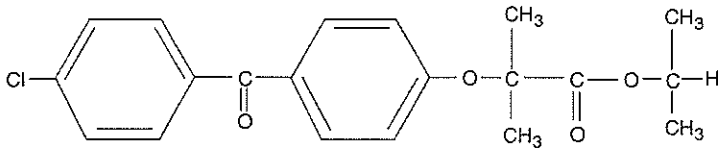
TRICOR® 48 mg and 145 mg

(fenofibrate tablets)

℞ only

DESCRIPTION

TRICOR (fenofibrate tablets), is a lipid regulating agent available as tablets for oral administration. Each tablet contains 48 mg or 145 mg of fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each tablet contains hypromellose 2910 (3cps), docusate sodium, sucrose, sodium lauryl sulfate, lactose monohydrate, silicified microcrystalline cellulose, crospovidone, and magnesium stearate.
In addition, individual tablets contain:

48 mg tablets: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum, D&C Yellow #10 aluminum lake, FD&C Yellow #6 /sunset yellow FCF aluminum lake, FD&C Blue #2 /indigo carmine aluminum lake.

145 mg tablets: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apoAI and apoAII.

The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor a (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).

The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after administration of three 48 mg or one 145 mg tablets are equivalent under fed conditions to one 200 mg capsule.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration.

Exposure to fenofibric acid in plasma, as measured by C_{max} and AUC, is not significantly different when a single 145 mg dose of fenofibrate is administered under fasting or nonfasting conditions.

Distribution

Upon multiple dosing of fenofibrate, fenofibric acid steady state is achieved within 9 days. Plasma concentrations of fenofibric acid at steady state are approximately double those following a single dose. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

Special Populations

Geriatrics

In elderly volunteers 77 - 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics

TRICOR has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal Insufficiency

The pharmacokinetics of fenofibric acid was examined in patients with mild, moderate, and severe renal impairment. Patients with severe renal impairment (creatinine clearance [CrCl] ≤ 30 mL/min) showed 2.7-fold increase in exposure for fenofibric acid and increased accumulation of fenofibric acid during chronic dosing compared to that of healthy subjects. Patients with mild to moderate renal impairment (CrCl 30-80 mL/min) had similar exposure but an increase in the half-life for fenofibric acid compared to that of healthy subjects. Based on these findings, the use of TRICOR should be avoided in patients who have severe renal impairment and dose reduction is required in patients having mild to moderate renal impairment.

Hepatic Insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Drug-drug Interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C8, CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption. (See **WARNINGS** and **PRECAUTIONS**).

Concomitant administration of fenofibrate (equivalent to TRICOR 145 mg) with pravastatin (40 mg) once daily for 10 days has been shown to increase the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3α-hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively in 23 healthy adults.

Concomitant administration of a single dose of fenofibrate (equivalent to 145 mg TRICOR) and a single dose of fluvastatin (40 mg) resulted in a small increase (approximately 15-16%) in exposure to (+)3R,5S-fluvastatin, the active enantiomer of fluvastatin.

A single dose of either pravastatin or fluvastatin had no clinically important effect on the pharmacokinetics of fenofibric acid.

Concomitant administration of fenofibrate (equivalent to TRICOR 145 mg) with atorvastatin (20 mg) once daily for 10 days resulted in approximately 17% decrease (range from 67% decrease to 44% increase) in atorvastatin AUC values in 22 healthy males. The atorvastatin C_{max} values were not significantly affected by fenofibrate. The pharmacokinetics of fenofibric acid were not significantly affected by atorvastatin.

Concomitant administration of fenofibrate (equivalent to TRICOR 145 mg) once daily for 10 days with glimepiride (1 mg tablet) single dose simultaneously with the last dose of fenofibrate resulted in a 35% increase in mean AUC of glimepiride in healthy subjects. Glimepiride C_{max} was not significantly affected by fenofibrate co-administration. There was no statistically significant effect of multiple doses of fenofibrate on glucose nadir or AUC with the baseline glucose concentration as the covariate after glimepiride administration in healthy volunteers. However, glucose concentrations at 24 hours remained statistically significantly lower after pretreatment with fenofibrate than with glimepiride alone. Glimepiride had no significant effect on the pharmacokinetics of fenofibric acid.

Concomitant administration of fenofibrate (54 mg) and metformin (850 mg) three times a day for 10 days resulted in no significant changes in the pharmacokinetics of fenofibric acid and metformin when compared with the two drugs administered alone in healthy subjects.

Concomitant administration of fenofibrate (equivalent to TRICOR 145 mg) once daily for 14 days with rosiglitazone tablet (rosiglitazone maleate) (8 mg) once daily for 5 days, Day 10 through Day 14, resulted in no significant changes in the pharmacokinetics of fenofibric acid and rosiglitazone when compared with the two drugs administered alone in healthy subjects.

Concomitant administration of fenofibrate (145 mg TRICOR) with ezetimibe (10 mg) once daily for 10 days to 18 healthy adults resulted in increases in total ezetimibe AUC, C_{max} and C_{min} of approximately 43%, 33% and 56%, respectively, and increases in ezetimibe glucuronide AUC, C_{max} and C_{min} of approximately 49%, 34% and 62%, respectively. The pharmacokinetics of fenofibric acid were not significantly affected by ezetimibe and the multiple-dose pharmacokinetics of free (unconjugated) ezetimibe were not significantly affected by fenofibrate.

Clinical Trials

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The effects of fenofibrate at a dose equivalent to 145 mg TRICOR (fenofibrate tablets) per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. TRICOR therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. TRICOR therapy also lowered triglycerides and raised HDL-C (see Table 1).

Table 1

Mean Percent Change in Lipid Parameters at End of Treatment†

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid values (n=646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n=361)	-18.7%*	-20.6%*	+11.0%*	-28.9%*
Placebo (n=285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type IIa)				
Mean baseline lipid values (n=334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n=193)	-22.4%*	-31.4%*	+9.8%*	-23.5%*
Placebo (n=141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL (Type IIb)				
Mean baseline lipid values (n=242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
All FEN (n=126)	-16.8%*	-20.1%*	+14.6%*	-35.9%*
Placebo (n=116)	-3.0%	-6.6%	+2.3%	+0.9%

† Duration of study treatment was 3 to 6 months.

* p = < 0.05 vs. Placebo

In a subset of the subjects, measurements of apo B were conducted. TRICOR treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type IV and V)

The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials[1] of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to TRICOR 145 mg per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

Table 2

Effects of TRICOR in Patients With Fredrickson Type IV/V Hyperlipidemia

Study 1	Placebo				TRICOR			
Baseline TG levels 350 to 499 mg/dL	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	28	449	450	-0.5	27	432	223	-46.2*
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1*
HDL Cholesterol	28	35	36	4	27	34	40	19.6*
LDL Cholesterol	28	120	129	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	-44.7*

Study 2	Placebo				TRICOR			
Baseline TG levels 500 to 1500 mg/dL	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)	N	Baseline (Mean)	Endpoint (Mean)	% Change (Mean)
Triglycerides	44	710	750	7.2	48	726	308	-54.5*
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4*

*= $p < 0.05$ vs. Placebo

The effect of TRICOR on cardiovascular morbidity and mortality has not been determined.

INDICATIONS AND USAGE

Treatment of Hypercholesterolemia

TRICOR is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia

TRICOR is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of TRICOR therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia[2].

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, thiazide diuretics and beta-blockers, are sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet. (See **WARNINGS** and **PRECAUTIONS**).

Fredrickson Classification of Hyperlipoproteinemias

		Lipid Elevation	
Type	Lipoprotein Elevated	Major	Minor
I (rare)	chylomicrons	TG	↑↔C
IIa	LDL	C	-
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C, TG	-
IV	VLDL	TG	↑↔C
V (rare)	chylomicrons, VLDL	TG	↑↔C

C = cholesterol
TG = triglycerides
LDL = low density lipoprotein
VLDL = very low density lipoprotein
IDL = intermediate density lipoprotein

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk > 20%)	< 100	≥ 100	≥ 130 (100-129:drug optional)††
2+ Risk Factors (10-year risk ≤ 20%)	< 130	≥ 130	10-year risk 10%-20%: ≥ 130 10-year risk < 10%: ≥ 160
0-1 Risk Factor†††	< 160	≥ 160	≥ 190 (160-189: LDL-lowering drug optional)

† CHD = coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

††† Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still >200 mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

CONTRAINDICATIONS

TRICOR is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

TRICOR is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

TRICOR is contraindicated in patients with preexisting gallbladder disease (see **WARNINGS**).

WARNINGS

Liver Function

Fenofibrate at doses equivalent to 96 mg to 145 mg TRICOR per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 96 mg to 145 mg TRICOR per day and was 0% in those receiving dosages equivalent to 48 mg or less TRICOR per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with TRICOR, and therapy discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis

Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. TRICOR therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants

Caution should be exercised when anticoagulants are given in conjunction with TRICOR because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

Concomitant HMG-CoA Reductase Inhibitors

The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

Concomitant administration of fenofibrate (equivalent to TRICOR 145 mg) and pravastatin (40 mg) once daily for 10 days increased the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3α-hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively. (See also **CLINICAL PHARMACOLOGY**, ***Drug-drug interactions***).

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including TRICOR, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving TRICOR and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, TRICOR therapy should be stopped.

Mortality

The effect of TRICOR on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

Other Considerations

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a 5-year randomized, placebo-controlled study of 9795 patients with type 2 diabetes mellitus treated with fenofibrate. Fenofibrate demonstrated a non-significant 11% relative reduction in the primary outcome of coronary heart disease events (hazard ratio [HR] 0.89, 95% CI 0.75-1.05, p=0.16) and a significant 11% reduction in the secondary outcome of total cardiovascular disease events (HR 0.89 [0.80-0.99], p=0.04). There was a non-significant 11% (HR 1.11 [0.95, 1.29], p=0.41) and 19% (HR 1.19 [0.90, 1.57], p=0.22) increase in total and coronary heart disease mortality, respectively, with fenofibrate as compared to placebo.

In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between TRICOR (fenofibrate tablets), Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to TRICOR.

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95%

confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group. (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs. 0/317, p=0.029).

PRECAUTIONS

Initial Therapy

Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting TRICOR therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Continued Therapy

Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of TRICOR. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 145 mg per day.

Pancreatitis

Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Hypersensitivity Reactions

Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs. 0%, and rash in 1.4 vs. 0.8% of fenofibrate and placebo patients respectively in controlled trials.

Hematologic Changes

Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of TRICOR administration.

Skeletal Muscle

The use of fibrates alone, including TRICOR, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Venothromboembolic Disease

In the FIELD trial, pulmonary embolus (PE) and deep vein thrombosis (DVT) were observed at higher rates in the fenofibrate- than the placebo-treated group. Of 9,795 patients enrolled in FIELD, there were 4,900 in the placebo group and 4,875 in the fenofibrate group. For DVT, there were 48 events (1%) in the placebo group and 67 (1%) in the fenofibrate group ($p = 0.074$); and for PE, there were 32 (0.7%) events in the placebo group and 53 (1%) in the fenofibrate group ($p = 0.022$).

In the Coronary Drug Project, a higher proportion of the clofibrate group experienced definite or suspected fatal or nonfatal pulmonary embolism or thrombophlebitis than the placebo group (5.2% vs. 3.3% at five years; $p < 0.01$).

Serum Creatinine

Elevations in serum creatinine have been reported in patients on fenofibrate. These elevations tend to return to baseline following discontinuation of fenofibrate. The clinical significance of these observations is unknown.

Drug Interactions

Oral Anticoagulants

CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRICOR. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING

COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.

HMG-CoA Reductase inhibitors

The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

Resins

Since bile acid sequestrants may bind other drugs given concurrently, patients should take TRICOR at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

Cyclosporine

Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including TRICOR, there is a risk that an interaction will lead to deterioration. The benefits and risks of using TRICOR (fenofibrate tablets) with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, rats were dosed with fenofibrate at 10, 45, and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD), based on body surface area comparisons (mg/m^2). At a dose of 200 mg/kg/day (at 6 times the MRHD), the incidence of liver carcinomas was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males. In a second 24-month rat carcinogenicity study in a different strain of rats, doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD.

A 117-week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg/day; 2 times the human dose), and gemfibrozil (250 mg/kg/day; 2 times the human dose, based on mg/m^2 surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular carcinoma and pancreatic acinar adenomas in males and hepatic neoplastic nodules in females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in males.

In a 21-month study in mice, fenofibrate 10, 45, and 200 mg/kg/day (approximately 0.2, 1, and 3 times the MRHD on the basis of mg/m^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18-month study at 10, 60, and 200 mg/kg/day, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis in primary rat hepatocytes.

In fertility studies rats were given oral dietary doses of fenofibrate, males received 61 days prior to mating and females 15 days prior to mating through weaning which resulted in no adverse effect on fertility at doses up to 300 mg/kg/day (~10 times the MRHD, based on mg/m^2 surface area comparisons).

Pregnancy

Pregnancy Category C

Safety in pregnant women has not been established. There are no adequate and well controlled studies of fenofibrate in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In female rats given oral dietary doses of 15, 75, and 300 mg/kg/day of fenofibrate from 15 days prior to mating through weaning, maternal toxicity was observed at 0.3 times the MRHD, based on body surface area comparisons; mg/m^2.

In pregnant rats given oral dietary doses of 14, 127, and 361 mg/kg/day from gestation day 6-15 during the period of organogenesis, adverse developmental findings were not observed at 14 mg/kg/day (less than 1 times the MRHD, based on body surface area comparisons; mg/m^2). At higher multiples of human doses evidence of maternal toxicity was observed.

In pregnant rabbits given oral gavage doses of 15, 150, and 300 mg/kg/day from gestation day 6-18 during the period of

organogenesis and allowed to deliver, aborted litters were observed at 150 mg/kg/day (10 times the MRHD, based on body surface area comparisons: mg/m2). No developmental findings were observed at 15 mg/kg/day (at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2).

In pregnant rats given oral dietary doses of 15, 75, and 300 mg/kg/day from gestation day 15 through lactation day 21 (weaning), maternal toxicity was observed at less than 1 times the MRHD, based on body surface area comparisons; mg/m^2.

Nursing Mothers

It is not known whether fenofibrate is excreted into milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fenofibrate, a decision should be made whether to discontinue nursing or administration of fenofibrate taking into account the importance of the drug to the lactating woman.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Fenofibric acid exposure is not influenced by age. However, elderly patients have a higher incidence of renal impairment, such that dose selection for the elderly should be made on the basis of renal function (see **CLINICAL PHARMACOLOGY, Special Populations, *Renal Insufficiency***). Elderly patients with normal renal function should require no dose modifications.

ADVERSE REACTIONS

Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM **Adverse Event**	**Fenofibrate*** **(N=439)**	**Placebo** **(N=365)**
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%
SGOT Increased	3.4%**	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 145 mg TRICOR.

** Significantly different from Placebo.

Additional adverse events reported during post-marketing surveillance or by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

Body as a Whole

Accidental injury, allergic reaction, chest pain, cyst, fever, hernia, infection, malaise and pain (unspecified).

Cardiovascular System

Angina pectoris, arrhythmia, atrial fibrillation, cardiovascular disorder, coronary artery disorder, electrocardiogram abnormal, extrasystoles, hypertension, hypotension, migraine, myocardial infarct, palpitation, peripheral vascular disorder, phlebitis,

tachycardia, varicose vein, vascular disorder, vasodilatation, venous thromboembolic events (deep vein thrombosis, pulmonary embolus) and ventricular extrasystoles.

Digestive System
Anorexia, cholecystitis, cholelithiasis, colitis, diarrhea, duodenal ulcer, dyspepsia, eructation, esophagitis, flatulence, gastritis, gastroenteritis, gastrointestinal disorder, increased appetite, jaundice, liver fatty deposit, nausea, pancreatitis, peptic ulcer, rectal disorder, rectal hemorrhage, tooth disorder and vomiting.

Endocrine System
Diabetes mellitus.

Hemic and Lymphatic System
Anemia, ecchymosis, eosinophilia, leukopenia, lymphadenopathy, and thrombocytopenia.

Laboratory Investigations
Alkaline phosphatase increased, bilirubin increased, blood urea nitrogen increased, serum creatinine increased, gamma glutamyl transpeptidase increased, lactate dehydrogenase increased, SGOT and SGPT increased.

Metabolic and Nutritional Disorders
Edema, gout, hyperuricemia, hypoglycemia, peripheral edema, weight gain, and weight loss.

Musculoskeletal System
Arthralgia, arthritis, arthrosis, bursitis, joint disorder, leg cramps, myalgia, myasthenia, myositis, rhabdomyolysis and tenosynovitis.

Nervous System
Anxiety or nervousness, depression, dizziness, dry mouth, hypertonia, insomnia, libido decreased, neuralgia, paresthesia, somnolence and vertigo.

Respiratory System
Allergic pulmonary alveolitis, asthma, bronchitis, cough increased, dyspnea, laryngitis, pharyngitis, pneumonia and sinusitis.

Skin and Appendages
Acne, alopecia, contact dermatitis, eczema, fungal dermatitis, herpes simplex, herpes zoster, maculopapular rash, nail disorder, photosensitivity reaction, pruritus, rash, sweating, skin disorder, skin ulcer and urticaria.

Special Senses
Abnormal vision, amblyopia, cataract specified, conjunctivitis, ear pain, eye disorder, otitis media and refraction disorder.

Urogenital System
Abnormal kidney function, cystitis, dysuria, gynecomastia, prostatic disorder, unintended pregnancy, urinary frequency, urolithiasis and vaginal moniliasis.

OVERDOSAGE

There is no specific treatment for overdose with TRICOR. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving TRICOR, and should continue this diet during treatment with TRICOR. TRICOR tablets can be given without regard to meals.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of TRICOR is 145 mg per day.

For adult patients with hypertriglyceridemia, the initial dose is 48 to 145 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 145 mg per day.

Treatment with TRICOR should be initiated at a dose of 48 mg/day in patients having mild to moderately impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of TRICOR if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

TRICOR® (fenofibrate tablets) is available in two strengths:

48 mg yellow tablets, imprinted with ⊐ and Abbo-Code identification letters "FI", available in bottles of 90 (**NDC** 0074-6122-90).

145 mg white tablets, imprinted with ⊐ and Abbo-Code identification letters "FO", available in bottles of 90 (**NDC** 0074-6123-90).

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep out of the reach of children. Protect from moisture.

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Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A. by Fournier Laboratories Ireland Limited, Anngrove, Carrigtwohill Co. Cork, Ireland or Laboratories Fournier SA, Rue de Pres Potets, 21121 Fontaine-les-Dijon, France.

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Diabetes Care

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Diabetes Care 30:S4-S41, 2007
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Position Statements
Position Statement

Standards of Medical Care in Diabetes—2007

American Diabetes Association

Abbreviations: ABI, ankle-brachial index • AMI, acute myocardial infarction • ARB, angiotensin receptor blocker • CAD, coronary artery disease • CBG, capillary blood glucose • CHD, coronary heart disease • CHF, congestive heart failure • CKD, chronic kidney disease • CMS, Centers for Medicare and Medicaid Services • CSII, continuous subcutaneous insulin infusion • CVD, cardiovascular disease • DCCB, dihydropyridine calcium channel blocker • DCCT, Diabetes Control and Complications Trial • DKA, diabetic ketoacidosis • DMMP, diabetes medical management plan • DPN, distal symmetric polyneuropathy • DPP, Diabetes Prevention Program • DRI, dietary reference intake • DRS, Diabetic Retinopathy Study • DSME, diabetes self-management education • DSMT, diabetes self-management training • ECG, electrocardiogram • ESRD, end-stage renal disease • ETDRS, Early Treatment Diabetic Retinopathy Study • FDA, Food and Drug Administration • FPG, fasting plasma glucose • GDM, gestational diabetes mellitus • GFR, glomerular filtration rate • HRC, high-risk characteristic • ICU, intensive care unit • IFG, impaired fasting glucose • IGT, impaired glucose tolerance • MNT, medical nutrition therapy • NDEP, National Diabetes Education Program • NPDR, nonproliferative diabetic retinopathy • OGTT, oral glucose tolerance test • PAD, peripheral arterial disease • PDR, proliferative diabetic retinopathy • PPG, postprandial plasma glucose • RDA, recommended dietary allowance • SMBG, self-monitoring of blood glucose • TZD, thiazolidinedione • UKPDS, U.K. Prospective Diabetes Study

INTRODUCTION

Diabetes is a chronic illness that requires continuing medical care and patient self-management education to

prevent acute complications and to reduce the risk of long-term complications. Diabetes care is complex and requires that many issues, beyond glycemic control, be addressed. A large body of evidence exists that supports a range of interventions to improve diabetes outcomes.

These standards of care are intended to provide clinicians, patients, researchers, payors, and other interested individuals with the components of diabetes care, treatment goals, and tools to evaluate the quality of care. While individual preferences, comorbidities, and other patient factors may require modification of goals, targets that are desirable for most patients with diabetes are provided. These standards are not intended to preclude more extensive evaluation and management of the patient by other specialists as needed. For more detailed information, refer to refs. 1–3.

The recommendations included are diagnostic and therapeutic actions that are known or believed to favorably affect health outcomes of patients with diabetes. A grading system (Table 1), developed by the American Diabetes Association (ADA) and modeled after existing methods, was utilized to clarify and codify the evidence that forms the basis for the recommendations. The level of evidence that supports each recommendation is listed after each recommendation using the letters A, B, C, or E.

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Table 1— ADA evidence grading system for clinical practice recommendations

I. CLASSIFICATION AND DIAGNOSIS

A. Classification

In 1997, ADA issued new diagnostic and classification criteria (4); in 2003, modifications were made regarding the diagnosis of impaired fasting glucose (IFG) (5). The classification of diabetes includes four clinical classes:

- Type 1 diabetes (results from ß-cell destruction,

usually leading to absolute insulin deficiency)
- Type 2 diabetes (results from a progressive insulin secretory defect on the background of insulin resistance)
- Other specific types of diabetes due to other causes, e.g., genetic defects in ß-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug or chemical induced (such as in the treatment of AIDS or after organ transplantation)
- Gestational diabetes mellitus (GDM) (diagnosed during pregnancy)

Some patients cannot be clearly classified as type 1 or type 2 diabetes. Clinical presentation and disease progression vary considerably in both types of diabetes. Occasionally, patients who otherwise have type 2 diabetes may present with ketoacidosis. Similarly, patients with type 1 may have a late onset and slow (but relentless) progression of disease despite having features of autoimmune disease. Such difficulties in diagnosis may occur in children, adolescents, and adults. The true diagnosis may become more obvious over time.

B. Diagnosis

Recommendations

- The FPG is the preferred test to diagnose diabetes in children and nonpregnant adults. (E)
- Use of the A1C for the diagnosis of diabetes is not recommended at this time. (E)

Criteria for the diagnosis of diabetes in nonpregnant adults are shown in Table 2. Three ways to diagnose diabetes are available, and each must be confirmed on a subsequent day unless unequivocal symptoms of hyperglycemia are present. Although the 75-g oral glucose tolerance test (OGTT) is more sensitive and modestly more specific than fasting plasma glucose (FPG) to diagnose diabetes, it is poorly reproducible and rarely performed in practice. Because of ease of use, acceptability to patients, and lower cost, the FPG is the preferred diagnostic test. It should be noted that the vast majority of people who meet diagnostic criteria for diabetes by OGTT, but not by FPG, will have an A1C value <7.0%. The use of the A1C for the diagnosis of diabetes is not recommended at this time.

View this table: Table 2— Criteria for the diagnosis of diabetes
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Hyperglycemia not sufficient to meet the diagnostic criteria for diabetes is categorized as either IFG or

impaired glucose tolerance (IGT), depending on whether it is identified through an FPG or an OGTT:

- IFG = FPG 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l)
- IGT = 2-h plasma glucose 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11.0 mmol/l)

Recently, IFG and IGT have been officially termed "pre-diabetes." Both categories, IFG and IGT, are risk factors for future diabetes and cardiovascular disease (CVD).

In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The OGTT is not recommended for routine clinical use but may be required in the evaluation of patients with IFG (see text) or when diabetes is still suspected despite a normal FPG, as with the postpartum evaluation of women with GDM.

II. SCREENING FOR DIABETES

Recommendations

- Screening to detect pre-diabetes (IFG or IGT) and diabetes should be considered in individuals ≥45 years of age, particularly in those with a BMI ≥25 kg/m^2. Screening should also be considered for people who are <45 years of age and are overweight if they have another risk factor for diabetes (Table 3). Repeat testing should be carried out at 3-year intervals. (E)
- Screen for pre-diabetes and diabetes in high-risk, asymptomatic, undiagnosed adults and children within the health care setting. (E)
- To screen for diabetes/pre-diabetes, either an FPG test or 2-h OGTT (75-g glucose load) or both are appropriate. (B)
- An OGTT may be considered in patients with IFG to better define the risk of diabetes. (E)

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Table 3— Criteria for testing for diabetes in asymptomatic adult individuals

There is a major distinction between diagnostic testing and screening. Both utilize the same clinical

tests, which should be done within the context of the health care setting. When an individual exhibits symptoms or signs of the disease, diagnostic tests are performed, and such tests do not represent screening. The purpose of screening is to identify asymptomatic individuals who are likely to have diabetes or pre-diabetes. Separate diagnostic tests using standard criteria are required after positive screening tests to establish a definitive diagnosis as described above.

Type 1 diabetes

Generally, people with type 1 diabetes present with acute symptoms of diabetes and markedly elevated blood glucose levels. Because of the acute onset of symptoms, most cases of type 1 diabetes are detected soon after symptoms develop. Widespread clinical testing of asymptomatic individuals for the presence of autoantibodies related to type 1 diabetes cannot be recommended at this time as a means to identify individuals at risk. Reasons for this include the following: *1*) cutoff values for some of the immune marker assays have not been completely established in clinical settings; *2*) there is no consensus as to what action should be taken when a positive autoantibody test result is obtained; and *3*) because the incidence of type 1 diabetes is low, testing of healthy children will identify only a very small number (<0.5%) who at that moment may be "pre-diabetic." Clinical studies are being conducted to test various methods of preventing type 1 diabetes in high-risk individuals (e.g., siblings of type 1 diabetic patients). These studies may uncover an effective means of preventing type 1 diabetes, in which case targeted screening may be appropriate in the future.

Type 2 diabetes

Type 2 diabetes is frequently not diagnosed until complications appear, and approximately one-third of all people with diabetes may be undiagnosed. Individuals at high risk should be screened for diabetes and pre-diabetes. Criteria for testing for diabetes in asymptomatic, undiagnosed adults are listed in Table 3. The effectiveness of early diagnosis through screening of asymptomatic individuals has not been determined (6).

Screening should be carried out within the health care setting. Either an FPG test or 2-h OGTT (75-g glucose load) is appropriate. The 2-h OGTT identifies people with IGT, and thus, more people are at increased risk for the development of diabetes and CVD. It should be noted that the two tests do not necessarily detect the same individuals (7). It is important to recognize that although the efficacy of interventions for primary prevention of type 2 diabetes have been demonstrated among individuals with IGT (8–10), such data among individuals with IFG (who do not also have IGT) are not available. The FPG test is more convenient to patients, more reproducible, less costly, and easier to administer than the 2-h OGTT (4,5). Therefore, the recommended initial screening test for nonpregnant adults is the FPG. An OGTT may be considered in patients with IFG to better define the risk of diabetes.

The incidence of type 2 diabetes in adolescents has increased dramatically in the last decade. Consistent with screening recommendations for adults, only children and youth at increased risk for the presence or the development of type 2 diabetes should be tested (11) (Table 4).

View this table: Table 4— Testing for type 2 diabetes in children

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The effectiveness of screening may also depend on the setting in which it is performed. In general, community screening outside a health care setting may be less effective because of the failure of people with a positive screening test to seek and obtain appropriate follow-up testing and care or, conversely, to ensure appropriate repeat testing for individuals who screen negative. That is, screening outside of clinical settings may yield abnormal tests that are never discussed with a primary care provider, low compliance with treatment recommendations, and a very uncertain impact on long-term health. Community screening may also be poorly targeted, i.e., it may fail to reach the groups most at risk and inappropriately test those at low risk (the worried well) or even those already diagnosed (12,13).

On the basis of expert opinion, screening should be considered by health care providers at 3-year intervals beginning at age 45, particularly in those with BMI ≥25 kg/m^2. The rationale for this interval is that false negatives will be repeated before substantial time elapses, and there is little likelihood of an individual developing any of the complications of diabetes to a significant degree within 3 years of a negative screening test result. Testing should be considered at a younger age or be carried out more frequently in individuals who are overweight and have one or more of the other risk factors for type 2 diabetes.

III. DETECTION AND DIAGNOSIS OF GDM

Recommendations

- Screen for diabetes in pregnancy using risk factor analysis and, if appropriate, use of an OGTT. (C)
- Women with GDM should be screened for diabetes 6–12 weeks postpartum and should be followed up with subsequent screening for the development of diabetes or pre-diabetes. (E)

Risk assessment for GDM should be undertaken at the first prenatal visit. Women with clinical characteristics consistent with a high risk for GDM (e.g., those with marked obesity, personal history of GDM or delivery of a previous large-for-gestation-age infant, glycosuria, polycystic ovary syndrome, or a strong family history of diabetes) should undergo glucose testing as soon as possible (14). An FPG ≥126 mg/dl or a casual plasma glucose ≥200 mg/dl meets the

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threshold for the diagnosis of diabetes and needs to be confirmed on a subsequent day as soon as possible unless unequivocal symptoms of hyperglycemia are present. High-risk women not found to have GDM at the initial screening and average-risk women should be tested between 24 and 28 weeks of gestation. Testing should follow one of two approaches:

- One-step approach: perform a diagnostic 100-g OGTT
- Two-step approach: perform an initial screening by measuring the plasma or serum glucose concentration 1 h after a 50-g oral glucose load (glucose challenge test) and perform a diagnostic 100-g OGTT on that subset of women exceeding the glucose threshold value on the glucose challenge test. When the two-step approach is used, a glucose threshold value ≥140 mg/dl identifies ~80% of women with GDM, and the yield is further increased to 90% by using a cutoff of ≥130 mg/dl.

Diagnostic criteria for the 100-g OGTT are as follows: ≥95 mg/dl fasting, ≥180 mg/dl at 1 h, ≥155 mg/dl at 2 h, and ≥140 mg/dl at 3 h. Two or more of the plasma glucose values must be met or exceeded for a positive diagnosis. The test should be done in the morning after an overnight fast of 8–14 h. The diagnosis can be made using a 2-h, 75-g glucose tolerance test, but that test is not as well validated for detection of at-risk infants or mothers as the 3-h, 100-g OGTT.

Low-risk status requires no glucose testing, but this category is limited to those women meeting all of the following characteristics:

- Age <25 years
- Weight normal before pregnancy
- Member of an ethnic group with a low prevalence of diabetes
- No known diabetes in first-degree relatives
- No history of abnormal glucose tolerance
- No history of poor obstetric outcome

Because women with a history of GDM have an increased subsequent risk for diabetes, they should be screened for diabetes 6–12 weeks postpartum and should be followed up with subsequent screening for the development of diabetes or pre-diabetes. For information on the National Diabetes Education Program (NDEP) campaign to prevent type 2 diabetes in women with GDM, go to www.ndep.nih.gov/diabetes/pubs/NeverTooEarly_Tipsheet.pdf.

▶ IV. PREVENTION/DELAY OF TYPE 2 DIABETES

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Recommendations

- Individuals at high risk for developing diabetes need to become aware of the many benefits of

modest weight loss and participating in regular physical activity. (A)
- Patients with IGT should be given counseling on weight loss as well as instruction for increasing physical activity. (A) (Reimbursement for such counseling is encouraged.)
- Patients with IFG should be given counseling on weight loss as well as instruction for increasing physical activity. (E) (Reimbursement for such counseling is encouraged.)
- Follow-up counseling appears to be important for success. (B)
- Monitoring for the development of diabetes in those with pre-diabetes should be performed every 1–2 years. (E)
- Close attention should be given to, and appropriate treatment given for, other CVD risk factors (e.g., tobacco use, hypertension, dyslipidemia). (A)
- Because of possible side effects and cost, there is insufficient evidence to support the use of drug therapy. (E)

Many studies have shown that individuals at high risk for developing diabetes (those with IFG, IGT, or both) can be given a wide variety of interventions that significantly delay, and sometimes prevent, the onset of diabetes (8–10,15–18). An intensive lifestyle modification program has been shown to be very effective (~58% reduction after 3 years). Use of the pharmacologic agents metformin, acarbose, orlistat, and rosiglitazone has also been shown to decrease incident diabetes to various degrees. Of note, however, each of these drugs may cause side effects of varying severity in a small number of individuals.

Lifestyle modification

In well-controlled studies that included a lifestyle intervention arm, substantial efforts were necessary to achieve only modest changes in weight and exercise, but those changes were sufficient to achieve an important reduction in the incidence of diabetes. In the DPP lifestyle group, a low-fat (<25% fat) intake was recommended; if reducing fat did not produce weight loss to goal, calorie restriction was also recommended. Participants weighing 120–174 lb (54–78 kg) at baseline were instructed to follow a 1,200 kcal/day diet (33 g fat), those 175–219 lb (79–99 kg) were instructed to follow a 1,500 kcal/day diet (42 g fat), those 220–249 lb (100–113 kg) were instructed to follow an 1,800 kcal/day diet (50 g fat), and those >250 lb (114 kg) were instructed to follow a 2,000 kcal/day diet (55 g fat). On average, 50% of the lifestyle group achieved the goal of ≥7% weight reduction and 74% maintained at least 150 min/week of moderately intense activity (8). In the Finnish Diabetes Prevention Study, weight loss averaged 9.2 lb at 1 year, 7.7 lb after 2 years, and 4.6 lb after 5 years (9); "moderate exercise," such as brisk walking, for 30 min/day was suggested. In the Finnish study, there was a direct relationship

between adherence with the lifestyle intervention and the reduced incidence of diabetes.

Lifestyle or medication?

Many factors must be considered when undertaking the effort to modify the course of glucose intolerance. Lifestyle modification may have other beneficial effects (e.g., reduced CVD), but is often very difficult to sustain, and its cost-effectiveness is questionable if the regimen is similar to what was employed in clinical trials. Even so, lifestyle intervention still may be cost-effective compared with some pharmacologic treatments. Drug therapy can be very costly (except for metformin, which is a generic drug), and side effects can range from mild/moderate discomfort to serious cardiovascular events. Finally, whether diabetes prevention efforts can, over the long term, influence the development of micro- or macrovascular events is unknown. It is possible that at least microvascular complications will be delayed or diminished, since they are more closely related to hyperglycemia.

In light of the above, health care professionals should first actively counsel patients to maintain normal weight and exercise regularly (even before glucose intolerance occurs). Because of potential side effects and cost, there is insufficient evidence to support the use of drug therapy as a substitute for, or routinely used in addition to, lifestyle modification to prevent diabetes. Public health messages, health care professionals, and health care systems should all encourage behavior changes to achieve a healthy lifestyle. Further research is necessary to understand how to better facilitate effective and efficient programs for the primary prevention of type 2 diabetes.

An ADA consensus statement offering more comprehensive guidance on diabetes prevention will be published in 2007.

V. DIABETES CARE

A. Initial evaluation

A complete medical evaluation should be performed to classify the patient, detect the presence or absence of diabetes complications, assist in formulating a management plan, and provide a basis for continuing care. If the diagnosis of diabetes has already been made, the evaluation should review the previous treatment and the past and present degrees of glycemic control. Laboratory tests appropriate to the evaluation of each patient's general medical condition should be performed. A focus on the components of comprehensive care (Table 5) will assist the health care team to ensure optimal management of the patient with diabetes.

View this table: Table 5— Components of the comprehensive diabetes evaluation
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B. Management

People with diabetes should receive medical care from a physician-coordinated team. Such teams may include, but are not limited to, physicians, nurse practitioners, physician's assistants, nurses, dietitians, pharmacists, and mental health professionals with expertise and a special interest in diabetes. It is essential in this collaborative and integrated team approach that individuals with diabetes assume an active role in their care.

The management plan should be formulated as an individualized therapeutic alliance among the patient and family, the physician, and other members of the health care team. Any plan should recognize diabetes self-management education (DSME) as an integral component of care. In developing the plan, consideration should be given to the patient's age, school or work schedule and conditions, physical activity, eating patterns, social situation and personality, cultural factors, and presence of complications of diabetes or other medical conditions. A variety of strategies and techniques should be used to provide adequate education and development of problem-solving skills in the various aspects of diabetes management. Implementation of the management plan requires that each aspect is understood and agreed on by the patient and the care providers and that the goals and treatment plan are reasonable.

C. Glycemic control

1. Assessment of glycemic control.

Techniques are available for health providers and patients to assess the effectiveness of the management plan on glycemic control.

a. *Self-monitoring of blood glucose*

Recommendations

- Clinical trials using insulin that have demonstrated the value of tight glycemic control have used self-monitoring of blood glucose (SMBG) as an integral part of the management strategy. (A)
- SMBG should be carried out three or more times daily for patients using multiple insulin injections. (A)
- For patients using less frequent insulin injections or oral agents or medical nutrition therapy (MNT) alone, SMBG is useful in achieving glycemic goals. (E)

- To achieve postprandial glucose targets, postprandial SMBG may be appropriate. (E)
- Instruct the patient in SMBG and routinely evaluate the patient's technique and ability to use data to adjust therapy. (E)

The ADA's consensus statements on SMBG provide a comprehensive review of the subject (19,20). Major clinical trials assessing the impact of glycemic control on diabetes complications have included SMBG as part of multifactorial interventions, suggesting that SMBG is a component of effective therapy. SMBG allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved. Results of SMBG can be useful in preventing hypoglycemia and adjusting medications, MNT, and physical activity.

The frequency and timing of SMBG should be dictated by the particular needs and goals of the patients. Daily SMBG is especially important for patients treated with insulin to monitor for and prevent asymptomatic hypoglycemia and hyperglycemia. For most patients with type 1 diabetes and pregnant women taking insulin, SMBG is recommended three or more times daily. The optimal frequency and timing of SMBG for patients with type 2 diabetes on oral agent therapy is not known but should be sufficient to facilitate reaching glucose goals. A recent meta-analysis of SMBG in non–insulin-treated patients with type 2 diabetes concluded that some regimen of monitoring was associated with a reduction in A1C of ~0.4%. However, many of the studies in this analysis also included patient education with diet and exercise counseling and, in some cases, pharmacologic intervention, making it very difficult to assess the contribution of SMBG alone to improved control (21). Patients with type 2 diabetes on insulin typically need to perform SMBG more frequently than those not using insulin. When adding to or modifying therapy, type 1 and type 2 diabetic patients should test more often than usual. The role of SMBG in stable diet–treated patients with type 2 diabetes is not known.

Because the accuracy of SMBG is instrument and user dependent (22), it is important for health care providers to evaluate each patient's monitoring technique, both initially and at regular intervals thereafter. In addition, optimal use of SMBG requires proper interpretation of the data. Patients should be taught how to use the data to adjust food intake, exercise, or pharmacological therapy to achieve specific glycemic goals. Health professionals should evaluate at regular intervals the patient's ability to use SMBG data to guide treatment.

b. *A1C*

Recommendations

- Perform the A1C test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control). (E)
- Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. (E)
- Use of point-of-care testing for A1C allows for timely decisions on therapy changes, when needed. (E)